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The water-soluble active principles of ergot.

By G. Barger and H. H. Dale.

About two years ago we called attention[1] to the fact that certain watery extracts of ergot possess a considerable physiological activity. Injected intravenously such extracts produce a considerable rise of arterial blood pressure, which cannot be attributed wholly to ergotoxine: for these extracts, unless injected in large quantities, do not, as a rule, produce the secondary abolition of the motor effects of sympathetic nerves, shown by us to be characteristic of ergotoxine. Moreover they retain almost all their activity on the blood pressure after treatment which removes what little ergotoxine they contain.

Recently, while engaged in investigating the pressor principles produced by putrefaction[2] we were struck by the similarity between the action of extracts from putrid meat and that of the preparations of ergot under discussion. This suggested the investigation of the latter by the methods which had proved successful in the case of the former.

Since one of the pressor substances produced by putrefaction was shown to be isoamylamine, we submitted an active watery extract of ergot to steam-distillation after making it alkaline. The distillate from 3 kilos of ergot, after suitable purification, finally yielded between 2 and 3 centigrammes of a crystalline oxalate melting at 162° C. Acid isoamylamine-oxalate melts at 169°, and the identity was further made extremely probable by the similarity in crystalline form, and the quantitative agreement in pressor action of the two substances. The amount of the volatile base thus probably identified was, however, insufficient to account for more than a very small part of the pressor action of the extract, which, indeed, retained most of its activity after exhaustive steam distillation.

We, therefore, further examined the ergot extract for the presence of *p.* hydroxyphenylethylamine, the most active of the pressor substances in putrid meat. By extraction from the neutralised extract with amylalcohol, and again from the latter with caustic soda, a solution was obtained containing practically the whole of the pressor substance.

[1] *Biochemical Journal*, II. p. 240. 1907.

[2] Barger and Walpole, This *Journal*, XXXVIII. p. 343. 1909.

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Further purification was effected by precipitation, in absolute alcoholic solution, with mercuric chloride. Excess of mercury being removed by sulphuretted hydrogen the filtrate yielded, to exhaustive extraction with ether, a powerfully active pressor base, soluble in water, giving an intense Millon reaction, and yielding a crystalline benzoyl-derivative which melted at 167° C.: mixed with an equal weight of synthetic dibenzoyl-*p.* hydroxyphenylethylamine (M. P. 170°) it melted at 168·5°. The benzoyl-derivative gave, on hydrolysis, a base, of which the physiological action corresponded closely to that of *p.* hydroxyphenylethylamine. The presence of this substance, the identification of which is thus complete, accounts for practically the whole of the pressor activity of watery extracts of ergot, except for such as is due to traces of ergotoxine. The method of standardising such extracts by their effect on the blood pressure, which has been widely used and recommended, is, therefore, practically an estimation of *p.* hydroxyphenylethylamine.

The details of the action of *p.* hydroxyphenylethylamine have been examined, in another connexion, by one of us in conjunction with Drs Dixon and Taylor, and the results are in course of publication. It may here be mentioned that the action of this substance on the uterus, like that on the vascular system, simulates the action of sympathetic nerves. Its presence in ergot extracts, therefore, accounts, even in the absence of ergotoxine, for that action of ergot which is most familiar in therapeutics.

There can be no doubt that the *p.* hydroxyphenylethylamine and the trace of isoamylamine are formed from tyrosine and leucine respectively: whether they are produced entirely by the ferments of the fungus itself or in any degree by bacterial action during the not sterile process of extraction, is a point on which we hope to procure evidence. In either case the notorious variability of the official liquid extract is readily intelligible.